## REMARKS

Introductory Comments:

Claims 1-40 were pending in the application. Applicants note with appreciation that the Office has acknowledged applicants' election of Group I (claims 1-32) and Species I (metal particles), as provided for in the Response filed 28 February 2002. Claims 33-40 have been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as drawn to a non-elected invention.

Accordingly, claims 1-32 were currently under consideration and were examined in the Office Action dated 20 May 2002. Applicants note with appreciation that the Office has withdrawn the following rejections: (1) the rejection of claims 1-40 under 35 U.S.C. §101 (provisional double patenting) over copending U.S. Patent Application No. 09/235,944; (2) the rejection of claims 1-32 under 35 U.S.C. §112, first paragraph as nonenabled; and (3) the rejection of claims 1-4, 11-12, 17, 19, 20-23 and 27 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,630,796 to Bellhouse et al. ("Bellhouse"). However, claims 1-32 remained rejected under 35 U.S.C. §103(a) as unpatentable over Bellhouse in view of U.S. Patent No. 5,962,477 to Mak ("Mak"). Applicants respectfully traverse the rejection.

Overview of the Amendment:

Applicants, by way of this Preliminary Amendment, have cancelled a single claim and made minor amendments to a single other claim. In particular, applicants have cancelled claim 19 without prejudice and disclaimer. It is to be understood that cancellation of this claim is not an acquiescence to ground of rejection or issue of patentability, and applicants reserve the right to bring the claim again in a subsequent, related application.



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In addition, applicants have amended claim 1 to now recite the limitations from claim 19. Support for the amendment can be found throughout the specification as originally filed, and in particular in original claim 19. Accordingly, no new matter has been added by way of this amendment, and the entry thereof is respectfully requested.

Pursuant to the Revised Notice from the USPTO, dated 13 February 2003, and entitled "Amendments May Now Be Submitted In Revised Format," the subject amendment has not been provided in both "clean version" and in "marked-up version" in conformance with 37 C.F.R. §1.121(b)(1) parts (ii) and (iii). Instead, this Preliminary Amendment includes a complete listing of all claims in the present application with an indication of the current status of each. The listing begins on a separate sheet and is captioned "CURRENT STATUS OF ALL CLAIMS IN THE APPLICATION".

The Rejections under 35 U.S.C. §103:

Claims 1-32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the disclosure of Bellhouse in view of Mak. In particular, the Office asserts that Bellhouse "teaches a needleless syringe for effective transdermal delivery of particles containing a therapeutic agent." Although the Office acknowledges that "[Bellhouse] does not teach topically positioning a transdermal drug delivery device or occlusive dressing comprising the therapeutic agent," the Office nonetheless concludes that "it is obvious .. to dress the site of the injection with an occlusive dressing or transdermal device after injection as a routine technique [and] including a therapeutic agent in the TTS flows logically from the transdermal delivery art." Office Action at page 3. The Office goes on to assert that Mak "teaches formulation for topical administration of therapeutic agents [in various forms]" and that these agents can be delivered using "active or passive transdermal patch[es], occlusive dressing[s] or transmucosal delivery device and absorption enhancer[s]." The Office further asserts that an "occlusive dressing [is] optionally applied to the skin after [application of] the therapeutic agent ... pretreatment



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of [an] area of skin upon which drug is to be placed prior to [application] of the transdermal patch ... [and] use of two separate dosage forms at the same time." Office Action pages 3-4, bridging paragraph. The Office then concludes that "it would have been obvious ... to apply a transdermal device of [Mak] containing the same or different drug." Office Action at page 4. Applicants respectfully disagree.

Section 2143 of the M.P.E.P. sets forth the following three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (1) the claimed invention must be considered as a whole; (2) the references must be considered as a whole and must suggest the desirability of making the combination; (3) the references must be viewed without the benefit of impermissible hindsight; and (4) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicant submits that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over its proposed combination of Bellhouse and Mak.

Initially, applicants draw the Office's attention to the amendment to claim 1, wherein the particles administered in step (a) of the method are delivered using a needleless syringe device. Claims 2-32 all depend, either directly or indirectly from claim 1, and thus contain this same base limitation. In the Advisory Action dated 17 December 2002, the Office had objected that "claim 1 is broad and reads on routine drug injection followed by application of a dressing containing antiseptic. No specific acceleration means or specific active agents [are recited]." Advisory Action, box 5. The amendment to claim 1 should eliminate this particular ground of rejection.

With regard to the Office's initial assertion set forth in the final Office Action dated 20 May 2002, that is, the assertion that even though Bellhouse does not teach,



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disclose or suggest topically positioning an occlusive dressing or transdermal delivery device, such a step would "be a routine technique" Office Action at page 3, and "injecting the particles of [Bellhouse] is logically followed by any kind of dressing, even if not disclosed" Office Action at page 5, applicants respectfully traverse. Initially, applicants note that the Office has not provided any support for its naked assertion that this step is merely a "routine technique." However, even more compelling is the fact that when one actually reads Bellhouse, one sees that Bellhouse et al. actually teach away from the Office's assertion. For example, Bellhouse et al. disclose their invention as being "useful for routine delivery of drugs, such as insulin ... could be of use in mass immunisation programs, or for the delivery of slow release drugs such as pain killers and contraceptives." Bellhouse, column 1, lines 45-54, emphasis added. Bellhouse go on to note that the "main advantages which flow from the invention include no needle and less pain, no risk of infection, delivery of drugs in natural solid form, quicker and safer to use than liquid drug, by syringe and needle and no sharps to dispose of." Bellhouse, column 1, lines 61-65. These features were contrasted with drug delivery by liquid jet which "caused skin damage and bleeding." Bellhouse, column 1, lines 58-60.

Accordingly, when the primary reference is read for what it actually discloses, it is clear that Bellhouse et al. considered their device useful for mere routine delivery of drugs, not some fancy transdermal delivery technique, and certainly not some multi-step drug delivery technique where multiple different drug delivery technologies are used to custom tailor drug delivery profiles (e.g., specially designed pharmacokinetics). Secondly, it is beyond argument that Bellhouse et al. never considered the use of their devices to administer strictly placebo particles, since the totality of the Bellhouse disclosure relates to delivery of therapeutics. In addition, Bellhouse et al. clearly emphasize that delivery of drugs using their device does not result in bleeding or pain. Accordingly, contrary to the Office's assertions, it is not "routine," "logical" or even sensible that one would place an occlusive dressing over the site of Bellhouse's delivery



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site. There would simply be no reason to apply a dressing to a site where a routine drug delivery step was carried out that resulted in no pain and no bleeding. What the Office has done is in effect rewrite the prior art, ignoring the clear teachings from that art, and arrived at an entirely inconsistent and unsupportable position. This is the very hallmark of an improper hindsight reconstruction of applicants' claimed invention.

Accordingly, the primary reference (Bellhouse) clearly teaches away from applicant's claimed invention. The Office's "logical" extensions of the Bellhouse disclosure contradict what Bellhouse actually teaches. The addition of the secondary reference (Mak) does nothing to overcome this basic and clear flaw in the Office's reasoning. As already noted in this case, Mak teaches that certain therapeutic agents can be used to modulate or prevent inflammatory/immune conditions. Mak teaches that their specified agents can be used to treat local or systemic inflammatory events, and that such agents can even be used to reduce inflammation events occurring as a result of traditional transdermal delivery devices (application of such patches to the skin can create irritation, inflammation and/or sensitization that is not beneficial). Mak fails to teach or even suggest applicants' particular recited combination, that is, the use of a particle delivery system in specific combinations with occlusion and/or transdermal delivery techniques to enhance drug delivery or establish a drug delivery profile simply not possible with any of the individual drug delivery systems.

The Office has selected specific portions of the Mak reference to support its assertion that Mak teaches applicants' recited methods. Office Action at page 4. These sections are as follows: **(1)** col. 5, lines 1-8; **(2)** col. 7, lines 17-25; **(3)** col. 42, lines 62-65; **(4)** col.43, lines 10-18; **(5)** col. 43, lines 33-34; **(6)** col. 46, lines 55-56; **(7)** col. 48, lines 18-20; **(8)** col.48, lines 54-56; **(9)** col. 52, lines 25-26; **(10)** col. 52, lines 38-44; **(11)** col. 53, lines 2-11; **(12)** col. 53, lines 37-46; **(13)** col. 55, lines 23-33; and **(14)** col. 59, lines 5-19. Applicants submit that the specified sections do not even come close to teaching or suggesting applicants' recited methods.



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In particular, the Office's first referenced section (1) is part of a table of contents. The section that it is taken from is "methods for modulation of the inflammatory/immune or TNF-mediated response"; subpart "chemical methods"; sub-subpart "other pharmacological agents." The actual text that the Office has pointed to reads "solutions, transdermal patches, occlusion, iontophoresis, sonophoresis, combinations, dosages and schedules." What Mak et al. thus teach is that their specific compositions (immune modulators, TNF agents) can be delivered via a number of well-known delivery techniques. The Office's second section (2) is taken from a definition of "drug", where the actual text reads "this includes therapeutic agents in all major therapeutic areas, also including proteins, peptides, oligonucleotides and carbohydrates as well as inorganic ions ...". Here, Mak et al. are again referring to their specific compositions. The Office's third section (3) it taken from the section headed "other pharmacological agents" and reads "additional pharmacological agents that can be delivered topically, transdermally, or iontophoretically according to the methods described herein include other cytokines, peptides, oligosaccharide, proteins and oligonucleotides capable of suppressing the production of TNF." Here, Mak et al. are clearly just referring to the various forms that their TNF or inflammatory modulating compositions can take, nothing more.

The Office's fourth section (4) appears under the heading "formulations" and reads "agents capable of modulating inflammation are applied to the skin, either iontophoretically, sonophoretically, topically, or through other routes of drug administration such as oral, intraperitoneal, intravenous, vaginal, rectal, intramuscular, aerosol ... [and] can be in a variety of different forms. These include, for example, solid, semi-solid, and liquid dosage forms, such as tablets, pills, powders, liquid solutions or suspensions, liposomes ...". Here, Mak et al. are merely listing a variety of different common drug delivery routes, and the generic form for drugs administered by these various routes. The Office's fifth section (5) appears under the same heading and reads "it is preferable to present [the active ingredient] as part of a pharmaceutical formulation.



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These formulations comprise the pharmacological agent in a therapeutically or pharmaceutically effective dose together with one or more pharmaceutically or therapeutically acceptable carriers and optionally other therapeutic ingredients." Mak et al. are referring here to standard pharmaceutical carriers such as water for injection and the like. The Office's sixth section **(6)** appears under the heading "transdermal patches" and reads "absorption enhancers can also be used to increase the flux of the compound across the skin." Absorption enhancers are known in the art and include chemicals classifed as lipid perturbants such as DMSO.

The Office's seventh section **(7)** appears under the heading "occlusion" and reads "occlusion comprises the application of a hydrated dressing, optionally with a pharmacological agent and a sealing material overlaid in the outside to the area of skin to be treated. Occlusion prevents loss of the drug from the skin, promotes skin hydration, and increases skin temperature." Accordingly, here Mak et al. are merely describing the attributes of skin occlusion. The Office's next section **(8)** appears under the heading "iontophoresis" and merely states that "some embodiments of the invention will employ the use of an electric field to administer a mixture of a therapeutic agent and a TNF inhibitor." The next two sections recited by the Office, **(9)** and **(10)** also appear under the heading "iontophoresis" and read "the inflammation, irritation, and/or sensitization which frequently occurs with transdermal or iontophoretic delivery of drugs and in other topical products such as cosmetics can be ameliorated by pre-, co- or post-administration of a TNF inhibitor," and "the TNF inhibitor can be used alone or in a combination of two or more. The agent or agents can be administered to the skin prophylactically, i.e., before the application of the iontophoretic current either topically or subcutaneously, or the agent or agent can be administered contemporaneously with the iontophoretic current." Here again, Mak et al. are discussing a well-known draw back with iontophoertic delivery, where inflammation or irritation due to the iontophoretic delivery is avoided with their recited anti-inflammatory agents.



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The Office's eleventh section (11) appears under the heading "combinations" and reads "combinations of the various techniques described herein, i.e., electrotransport, sonophoresis, pharmacological intervention and occlusion can also be utilized. For example, pharmacological agents can be administered "actively" through the use of iontophoresis or sonophoresis, optionally with stratum corneum lipid perturbants, or "passively" for example via the topical administration of pharmacological agents, alone or with stratum corneum lipid perturbants. A further embodiment will combine iontophoresis with occlusion." Here, Mak et al. discuss various drug administration techniques, and teach that topical or iontophoretic delivery can be enhanced with lipid perturbants (e.g., DMSO). The Office's next recited section (12) appears under the same heading, and reads "the patient may receive concurrent treatment with the various therapies, for example, an occlusive dressing containing the pharmacological agent my be applied to the affected area. Alternatively, the pharmacological agent may be delivered iontophoretically." Here, Mak et al. are discussing "concurrent" treatment methods, where apparently a topical administration takes place at the site of inflammation and a iontophoretic administration is carried out at a different site.

The last two sections cited by the Office (13) and (14) discuss the incorporation of a TNF inhibitor in, e.g., transdermal patch or ostomy device, in combination with other drugs, or the TNF inhibitor is applied to the site prior to or after fixing the transdermal patch, in order to reduce irritation and inflammation commonly encountered with transdermal delivery patches.

Accordingly, the Office has cited not less than 14 different sections of the Mak reference, where the authors merely discuss the use of TNF inhibitors or anti-inflammatory agents to reduce the side-effects commonly associated with transdermal patches. The Mak reference fails to teach, suggest or so much as hint at applicants' recited methods. There is no teaching whatsoever that one should administer a drug using particle injection techniques and then enhance drug delivery with the use of occlusive



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dressings, or combine the particle injection technique with a secondary drug delivery method to provide a different drug delivery profile, or use a placebo metallic particle as a pre-treatment step for a subsequent transdermal or topical delivery technique. The Office's assertion that Mak "teaches transdermal administration of antigen and adjuvant preceded by treatment of the area of application to accelerate drug delivery" (Office Action at page 5) is without basis. Applicants have reviewed all of the Office's cited sections of Mk in detail, and can find nothing to support this statement. Accordingly, no possible combination of Bellhouse and Mak can result in applicants' recited methods. There is simply no teaching or suggestion that even comes close to applicants' methods.

Furthermore, applicants note that Mak contains 85 columns of disclosure regarding different methods and apparatus for administering drugs. Mak published in October of 1999 and has an apparent 102(e) date that extends back to 1994. Bellhouse has a 102(e) date that extends back to 1993-1994. Accordingly, the fact that Mak provided such an exhaustive disclosure yet completely missed applicants' particle delivery techniques and particularly applicants' combination of particle delivery techniques with other drug delivery methods and apparatus speaks volumes. If, as the Office asserts, applicants' methods are so obvious from Bellhouse and Mak, yet both Bellhouse and Mak completely failed to teach or suggest applicants' methods, then what the Office has identified is actually a long-felt need in the art that was not met until applicants taught their combination. This long-felt need extended for 6 years until applicants made their surprising discovery. The presence of a long-felt need combined with the Office's asserted motivations is a clear indication of non-obviousness. *Graham v. John Deere Co.* 148 USPQ 459 (S. Ct. 1966).

For all of the foregoing reasons, then, applicants submit that the rejection of claims 1-32 under 35 U.S.C. §103(a) is improper. The Office has failed to identify in the prior art the requisite teaching or suggestion to arrive at applicants' claimed invention when that invention is considered as a whole as it must be under a Section 103 analysis.



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The Office has failed to establish a *prima facie* showing of obviousness over its cited combination since: (a) it has not identified the requisite suggestion or motivation to modify or combine the references in such a way as to arrive at applicants' unique combination; (b) there cannot have been a reasonable expectation of success for such a modification and/or combination since it was neither taught nor suggested; and (c) the cited references do not teach or suggest all the claim limitations when applicants' invention is considered as a whole. When the cited references are considered as a whole and viewed without the benefit of impermissible hindsight, it is clear that they simply fail to teach or suggest the desirability of making applicants' recited combination, and much less the actual combination. Reconsideration and withdrawal of the rejection is thus earnestly solicited.



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## CONCLUSION

Applicants respectfully submit that the claims as now pending define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect is earnestly solicited. Applicants further ask that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that the Examiner contact the undersigned in the UK at +44 1865 332 600.

Respectfully submitted,

Date: 17 June 2003

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